Systemic Vascular Resistance Guided Vasopressor Dose Titration in a Case of Vasodilator Shock Caused by Metformin

Mohamed Shirazy, MBBCh, MSc, MRCEM, EDIC* Karim Hakim, MBBCh, MSc, MD** Anis Chaari, MBBCh, MD, EDIC*** Kamel Bousselmi, MBBCh, MD, EDIC**** Vipin Katus, MBBCh, MD, EDIC***** Alaa Abdulaziz, BSPS, PharmD, BCPS, BCCCP****** Shaikha Aljawder, MBSc, MD, MBA*******

Vasodilator shock and metformin-associated lactic acidosis (MALA) are the worst adverse effects of metformin toxicity. Systemic vascular resistance (SVR) is known to be decreased in vasodilator shock. Accordingly, vasopressors are the treatment of choice of vasodilator shock; their effect is via increasing the SVR. Cardiac output can be measured accurately and non-invasively using transthoracic echocardiography (TTE).

A fifty-seven-year-old male patient was admitted with vasodilator shock induced by metformin toxicity. TTE was used to provide serial measurements of the SVR. Accordingly, vasopressor doses were titrated. The patient received vasopressor therapy, standard supportive medical treatment, in addition to continuous renal replacement therapy. On the sixth ICU day, epinephrine was weaned off, followed by nor-epinephrine on the tenth day. The patient was transferred to the ward by the fifteenth day.

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Metformin is a biguanide used as a first-line treatment for type 2 diabetes mellitus (DM). Several adverse effects have been reported; metformin-associated lactic acidosis (MALA) is the most life-threatening, which may present with a vasodilator shock characterized by decreased systemic vascular resistance (SVR)[1,2,3].

Norepinephrine is the drug of choice in vasodilatory shock. It increases the mean arterial blood pressure (MAP), cardiac index (CI), renal perfusion and systemic oxygen delivery[4,5].

Transthoracic echocardiography (TTE) is a non-invasive and reproducible bedside modality for hemodynamic monitoring of shocked patients, which can monitor the fluid resuscitation response and measure the cardiac output (CO)[6,7].

The aim of this case presentation is to highlight the usefulness of transthoracic echocardiography as a non-invasive modality in the titration of the vasopressor doses in cases of vasodilator shock.

THE CASE

A fifty-seven-year-old male presented after fainting. He had a history of type II Diabetes Mellitus (DM) and hypertension and he was on metformin and amlodipine. Moreover, he was an alcohol dependent. On presentation, the patient was drowsy with rapid shallow breathing. His vital signs were: blood pressure 80/40 mmHg, heart rate 38 beats/min, capillary refill time 6 seconds, respiratory rate 40 breaths/minute, SpO_2 85% on 100 % FiO2, and temperature 36 degrees Celsius. His venous blood gas showed a high anion gap metabolic acidosis with hyperlactatemia.

The patient was intubated and mechanically ventilated. He received an initial resuscitation of 2.5 liters of crystalloids together with intravenous (IV) atropine and antihyperkalemic measures followed by transcutaneous pacing. Norepinephrine infusion was commenced and titrated up to 2 mcg/kg/min after the insertion of central venous and intra-arterial catheters.

Transthoracic echocardiogram (TTE) revealed a preserved global systolic function (EF 57%) and a collapsible inferior vena cava. Accordingly, another fluid bolus of 2 liters of crystalloids was administered followed by epinephrine infusion that was titrated up to a dose of 2 mcg/min. However, the MAP and high lactate levels did not improve. The patient was admitted to the Intensive Care Unit (ICU), see table 1.

SVR was calculated after measuring the CO by TEE using the formula {80*(MAP-CVP)/CO}[13]. Guided by the serial measurements of SVR, both nor-epinephrine and epinephrine doses were titrated up to 4mcg/kg/min, and 4 mcg/min respectively, see figure 1.

* ICU Senior Registrar
** ICU Consultant
*** ICU Consultant
**** ICU Consultant
***** ICU Consultant
Department of Critical Care Medicine
****** Critical Care Clinical Pharmacist
Clinical Pharmacy Unit
******* Emergency Medicine Registrar
Department of Emergency Medicine
King Hamad University Hospital
Kingdom of Bahrain
E-mail: mohamed.shirazy@khuh.org.bh

Table 1: Laboratory Investigations

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Unit
Hb	12	13	11	10	9.9	10	9.8	8.9	9.2	10	9.6	8.7	9.5	10	9.9	g/Dl
WBC	10.7	9.08	7.62	11.2	9.3	12.2	17.9	14.2	12.8	8.73	9.69	9.82	7.85	7.49	7.52	$x10^9$/L
Platelets	155	143	152	120	99	110	92	146	183	211	231	250	241	278	423	$x10^9$/L
Urea	23	29	16	6	4	6	7.4	7.9	15.5	20.4	23.7	29.2	16.2	6.09	4.1	mmol/L
Creatinine	410	336	204	155	117	140	190	210	312	358	410	336	204	155	117	Umol/L
Na	128	144	143	140	139	138	142	142	137	136	135	136	140	141	144	mmol/L
K	6.35	3.5	4.5	4.4	4.2	4.4	3.36	4.14	4.5	4.05	4.08	3.4	3.82	3.88	4.1	mmol/L
ALT	38	42	41	39	48	31	21	25	25	29	29	28	29	27	26	U/L
AST	164	130	116	113	35	31	30	42	41	39	41	34	28	26	25	U/L
CK-MB	2.2	2.4	2.8	2.1	2.9	2.5	3.2	3.7	2.4	2.1	3.5	2.9	2.3	3.3	2.7	ug/L
Troponin I	0.03	0.04	0.02	0.06	0.02	0.05	0.03	0.05	0.04	0.06	0.02	0.04	0.03	0.06	0.04	ng/ml
INR	1.3	1.1	1	1.2	1	1	1	1.1	1.2	1	0.9	1	1.1	1	1	
aPTT	62	55	50	44	53	60	32	29	59	30	28	29	30	36	30	sec
Lactate	18.9	6.7	2.9	1.6	1.5	1.9	3	2.7	2	1.4	1.04	0.89	1.07	0.96	0.77	mmol/L
HCO_3	5.29	8.73	17.5	18.4	22.2	23	15	19	19.4	22	25.6	24.3	23	26.4	25.1	mmol/L
PH	6.9	7.19	7.34	7.42	7.44	7.39	7.25	7.32	7.42	7.45	7.46	7.44	7.41	7.46	7.43	
CRP	45	33	36	29	34	48	132	113	73	64	32	27	21	18	12	mg/L
PCT	0.2	0.4	0.1	0.3	0.2	0.9	3.6	2.2	0.6	0.3	0.2	0.1	0.1	0.1	0.1	

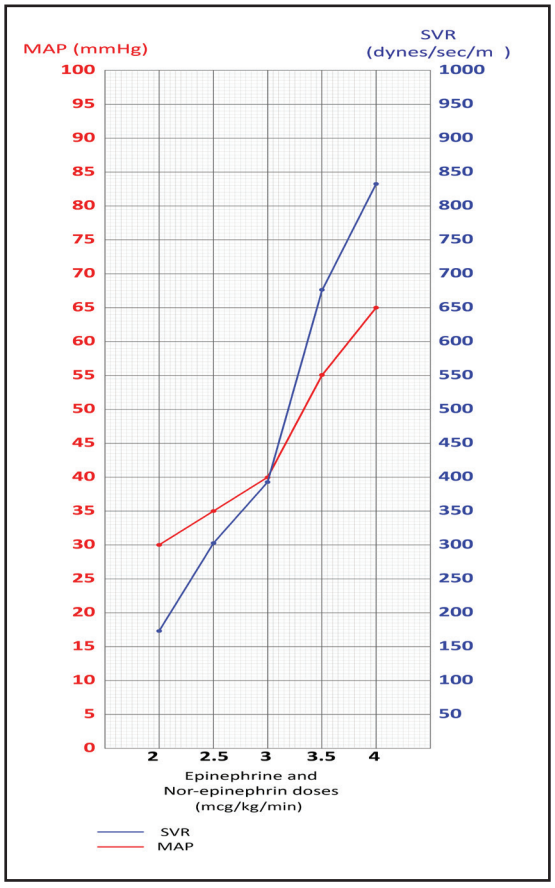

Figure 1: Nor-Epinephrine and Epinephrine Doses versus MAP and SVR

In addition to the standard supportive medical treatment; he received ninety hours of continuous renal replacement therapy (CRRT), see table 2.

Table 2: Compounds/Drugs Applied to the Patient

Compound/Drug	Dose	Starting Time	Duration
Nor-epinephrine	0.01-4 mcg/kg/min IV infusion	Day 1	10 days
Epinephrine	0.01-4 mcg/min IV infusion	Day 1	6 days
Hydrocortisone	200 mg/24hrs IV infusion	Day 1	9 days
Thiamine	100 mg/24hrs IV	Day 1	15 days
Omeprazole	40 mg/24hrs IV	Day 1	15 days
Heparin	5000 Units/12hrs IV	Day 1	15 days
Meropenem	1 g/12hrs IV	Day 7	7 days
Levofloxacin	250 mg/24hrs IV	Day 7	7 days
Vancomycin	1 g/12hrs IV	Day 7	7 days

On the sixth ICU day, epinephrine was weaned off, followed by nor-epinephrine on the tenth day. The patient was transferred to the ward by the fifteenth day.

DISCUSSION

MALA causes Type B lactic acidosis and vasodilatory shock. Therefore, vasoactive agents approaching high doses were reported to be required in addition to fluid resuscitation to preserve tissue perfusion[1,2].

Norepinephrine has a potent vasoconstrictive and weak inotropic effect. Epinephrine can be an add-on catecholamine in refractory shock as it has a strong vasoconstrictive and inotropic effect[4,5].

The recommended norepinephrine and epinephrine dose range from 0.01 to 3 mcg/kg/minute and 0.05 to 2 mcg/minute, respectively[9]. However, higher norepinephrine doses up to 5 mcg/kg/min were described in refractory vasodilator shock[10].

CO can be calculated using TTE by measuring the stroke volume (SV). TTE can measure the area of the left ventricular

outflow tract ($LVOT_{area}$), and the time velocity integral (TVI) in the left ventricular outflow tract (TVI_{LVOT}), using the formula [$SV=LVOT_{area}\times TVI_{LVOT}$]. Hence, CO can be measured. CO = SV × Heart Rate[6,7].

SVR is measured using the formula {80*(MAP-CVP)/CO}. It normally ranges from 800-1200 dynes·sec/cm[7].

In vasodilator shock, the SVR is reduced. Therefore, measuring the SVR helps in guiding the management using volume resuscitation, vasopressor, and inotropic agents' doses[3,4,7].

In this case, we adopted the TTE to quantify the degree of decrease in the SVR and subsequently adjusted the vasopressors' doses.

Several adverse effects as arrhythmias, peripheral ischemia, and skin necrosis were reported from the high doses of vasopressors[10]. In our case, no significant adverse effects were noticed, which may suggest that the known adverse effects may not be dose-dependent.

Studies revealed the usefulness of the bicarbonate buffered CRRT in the treatment of MALA[8]. In our case, continuous venovenous hemodiafiltration (CVVHDF) method was commenced early followed by a marked improvement in renal functions and lactic acidosis.

CONCLUSION

Our case highlights the usefulness of TEE in the measurement of SVR as a guide to titrate the vasopressors' doses to even higher doses than indicated.

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